NON-TECHNICAL ABSTRACT

Despite radical surgery, chemotherapy and radiation, glioblastoma patients have a poor prognosis with a median survival of approximately 36 weeks. Tumor cells in glioblastoma patients produce a substance, Transforming Growth Factor-ß2 (TGF-ß2), that suppresses immunity in patients. It has been postulated that inhibiting TGF-ß production of the tumor cells by genetic alteration may result in tumor cells becoming more immunogenic and suitable for use in immunizations. We have demonstrated the safety and efficacy of this approach in an animal tumor model. The animal model utilized in our studies is the rat 9L glioma. Like human gliomas, rat 9L glioma cells secrete the immuno-suppressor substance TGF-ß2. Immunization of tumor bearing rats with TGF-ß2 gene modified tumor cells resulted in eradication of intracranial tumors in 17 out of 17 treated animals. In contrast, immunizations with IL-2 secreting tumor cells only protected 3 out of 10 animals and immunizations with tumor cells that were modified with control vectors protected only 2 out of 15 animals. All animals in a control non-immunized group died within five weeks.

The goal of the current study is to examine the safety of subcutaneous injection of glioblastoma patients with different doses of tumor cells that have been genetically modified to block their secretion of TGF-ß2. In this Phase I Clinical Trial, tumor samples will be obtained from the patients at the time of clinically indicated surgery. The tumor samples will be grown in culture to establish a cell line for each patient. The cultured tumor cells will be genetically altered in the laboratory to inhibit their secretion of TGF-ß and injected into the patients. The first group of patients will be injected with five million irradiated TGF-ß2 gene modified tumor cells. Subsequently, in dose escalation studies the second group of patients will be injected with 10 million, and the third group with 20 million irradiated TGF-ß2 gene modified tumor cells. Each patient will receive four injections of the indicated number of the irradiated gene modified autologous tumor cells at approximately three week intervals. These studies will be performed by the UCLA comprehensive brain tumor team at the UCLA Medical Center. Following injections, patients will be observed for signs of toxicity and monitored for tumor growth. The results of this Phase I Clinical Trial will be used to assess the safety of this gene therapy. The studies may also provide preliminary data to evaluate the potential utility of this form of gene therapy in management of gliomas.